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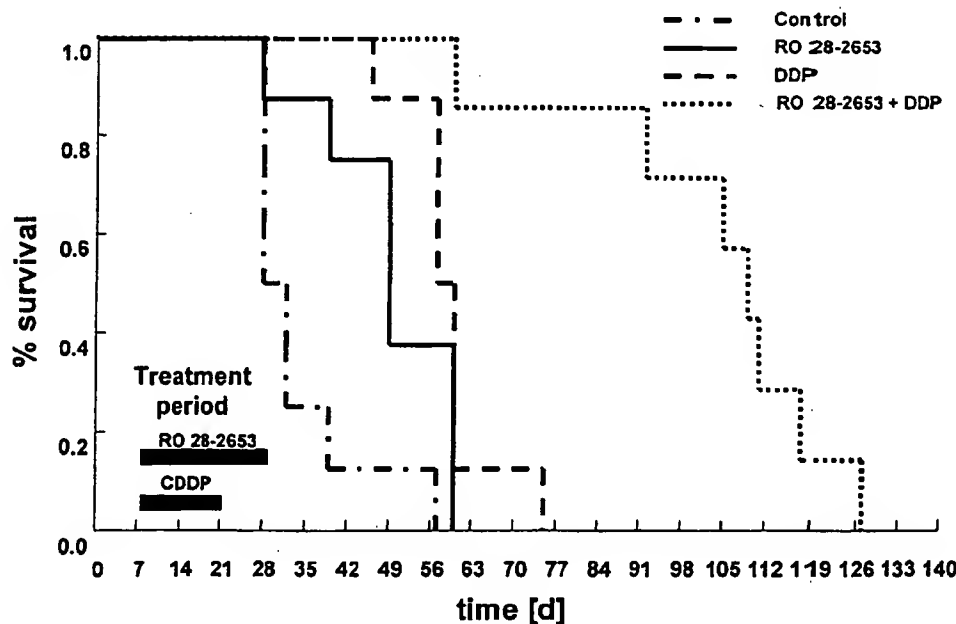
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(54) Title: COMBINATION OF A GELATINASE INHIBITOR AND AN ANTI-TUMOR AGENT, AND USES THEREOF



(57) Abstract: The invention concerns combinations of a gelatinase inhibitor, e.g. Ro-28-2653 with a cytotoxic/cytostatic agent and its use for the treatment of tumors.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Combination of a gelatinase inhibitor and an anti-tumor agent, and uses thereof

The present invention relates to composition and methods for the treatment of patients with solid metastasized or non-metastasized tumors. These are characterized by administration of a gelatinase inhibitor, e.g. RO 28-2653 in combination with a cytotoxic/cytostatic compound, e.g. Cisplatin, Paclitaxel, Gemcitabine or Etoposide.

Introduction

In modern clinical oncology, the biggest challenge for the successful treatment of patients is the problem of metastasis rather than the primary tumor itself. For tumor cells to be able to spread and form distant metastases several prerequisites have to be fulfilled. Among these one of the most important ones is the ability to grow invasively into the surrounding tissue, intravasate into the blood- or lymphatic vessel system and finally to extravasate and seed in the target tissue.

Recently a new class of molecules, namely the proteases, were identified to play a major role in this process. With the help of these enzymes tumor cells break down extracellular matrix proteins which are major constituents of connective tissue and basal membranes. Among these proteases the matrix metalloproteases (MMPs), and, more specifically, MMP-2 and MMP-9 (= gelatinases A and B) were identified as major contributors in this process of matrix degradation (Johansson et al., Cell. Mol. Life Sci. 57 (2000) 5-15). In addition, especially MMP-9 was found to play an important role in the formation of new blood vessels, a process called angiogenesis, which is essential for a tumor to establish and uphold a sufficient supply with nutrients and oxygen (Vu, T.H., et al., Cell 93 (1998) 411-422). Not surprisingly, indeed MMP-2 and/or MMP-9 were found to be overexpressed by a large proportion of individual tumors irrespective of histological origin.

Inhibition of MMPs, either with the naturally occurring Tissue Inhibitors of Metalloproteases (TIMPs), or with low molecular weight inhibitors, resulted in impressive anti-tumor and anti-metastatic effects in animal models (Brown, P.D., Medical Oncology 14 (1997) 1-10). Most of the low-molecular weight inhibitors of MMPs are derived from the hydroxamic acid compound class and inhibit MMPs in a broad manner, being not selective for MMP-2 and MMP-9, the key MMPs in

tumor invasion, metastatic spread, and angiogenesis. However, MMP inhibiting molecules from various other structural classes, e.g. the tri-oxo pyrimidines, have been described, e.g. in WO 97/23465 and WO 01/25217, which are incorporated by reference. A member of this class of compounds, RO 28-2653, is an extremely
5 potent, and highly selective, gelatinase inhibitor with an almost exclusive specificity for MMP-2, MMP-9, and MT1-MMP, the enzyme activating MMP-2, while sparing most other members of the MMP family of proteases. Ro 28-2653, with the chemical name 5-(4-biphenyl)-5-[N-(4-nitrophenyl) piperazinyl] barbituric acid is described in WO 97/23465.

10 Several MMP inhibitors, predominantly of the hydroxamic acid substance class were, and in part still are, in clinical testing. All of the published clinical results with these inhibitors were disappointing, showing little or no clinical efficacy (Fletcher, L., Nature Biotechnology 18 (2000) 1138-1139). The reason for this lack of efficacy in the clinic most likely is the fact that patients could not be given high enough
15 doses for anti-tumor or anti-metastatic activity because of the side effects associated with these broadly acting inhibitors. These dose-limiting side effects were predominantly arthralgias and myalgias (Drummond, A.H., et al., Ann. N.Y. Acad. Sci. 878 (1999) 228-235). As a possible way to circumvent this problem, the combination of MMP inhibitors with classical cytostatic/cytotoxic compounds was
20 evaluated in animal studies. Indeed, in these experiments, MMP inhibitors, in combination with cytostatic/cytotoxic drugs, showed enhanced efficacy (Giavazzi, R., et al., Clin. Cancer Res. 4 (1998) 985-992).

Ro 28-2653 is an MMP inhibitor with high selectivity for MMP-2 and MMP-9 and the treatment with this compound showed no side effects. Indeed, no side effects
25 similar to those observed with the broad-spectrum inhibitors were seen in toxicological tests over a wide range of doses. Thus, no dose-limiting toxicities were expected with RO 28-2653, and accordingly no additional benefit from co-treatment with cytostatic/cytotoxic drugs was expected. However, to explore also the distant possibility of an additional benefit from combination treatment, such
30 studies were initiated and conducted in various animal models. The models and cytostatic/cytotoxic drugs were chosen to reflect as broad a spectrum of oncological indications and clinically active treatment principles as possible.

Surprisingly, combinations of RO 28-2653 with cytostatic/cytotoxic compounds in various models of different histological origin clearly showed enhanced anti-tumor activity as compared to the respective single-agent treatments. Thus, in principle all human patients with solid metastasized or non-metastasized tumors, e.g. tumors of the lung, prostate, colon, breast, pancreas, ovary, skin, kidney, bladder, liver, head and neck, stomach, and brain are eligible for treatment with gelatinase inhibitors in combination with cytotoxic/cytostatic compounds.

The treatment with the gelatinase-inhibitor most likely will be a chronic treatment, starting either simultaneously with the combination partner or sequentially, i.e. before and after the treatment with the combination partner. In this context, simultaneous treatment means that the gelatinase inhibitor treatment takes place in parallel to, and is not stopped for, the necessary cycles of cytostatic/cytotoxic treatment, while sequential treatment means that the gelatinase inhibitor treatment is discontinued for the duration of the treatment with the cytostatic/cytotoxic drugs. The administration schedule depends on the tumor to be treated as well as on the cytostatic/cytotoxic agent to be used.

Preferred cytostatic/cytotoxic compounds are, for example: Cisplatin, Paclitaxel, Vinblastin, Mitomycin, Gemcitabine, Etoposide, Doxetaxel, Carboplatin, Irinotecan, Topotecan, Navelbine, Doxorubicin, Epirubicin, Oxaliplatin, 5-Fluoruracil, Capecitabine, 5-UFT, Herceptin, alpha interferon.

The administration of the gelatinase inhibitor will preferentially be oral, with doses ranging between 0.5 mg/kg and 50 mg/kg. Administration of the various combination partners will be as approved by the health authorities, which in most cases is by i.v. infusion. The partners used for the combination therapy can be contained in separate package format or together in a kit. Such a kit contains the i.v. preparations of the cytotoxic/cytostatic agents, e.g. ampoules and blister packages with tablets of the gelatinase inhibitors.

The following experimental part, references and figures are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Description of the Figures

- Figure 1 shows the effect of the combination of RO 28-2653 and Cisplatin on survival in the orthotopic HOC-22 ovarian cancer xenograft model. DDP = Cisplatin. Survival is displayed as Kaplan-Meier-Plot. Statistics was calculated using the log rank test. Animals were treated with RO 28-2653 for three weeks, from day 7 to day 21, with daily oral doses of 45 mg/kg six times a week. Cisplatin treatment consisted of 4 doses of 3 mg/kg i.v. per mouse once every 4 days, starting on day 7.
- Figure 2 shows the effect of the combination of RO 28-2653 and Paclitaxel on primary tumor size in the subcutaneous HCT116 CL5.5 colon cancer xenograft model.
- Figure 3 shows the effect of the combination of RO 28-2653 and Etoposide on the weight of primary tumors in the syngeneic orthotopic rat MatLyLu prostate cancer model. ■ Untreated Control ▼ Vehicle Control ◆ Etoposide ▲ RO 28-2653 • RO 28-2653 + Etoposide. — Mean tumor weight. Rats were treated with RO 28-2653 with daily oral doses of 100 mg/kg starting on day 6 after tumor implantation, until the penultimate day of the experiment (day 17). Etoposide was given intraperitoneally once daily, from day 6 to day 17, at a dose of 25 mg/m².

Experimental Part

Combination of RO 28-2653 with Cisplatin

The activity of RO 28-2653 in combination with Cisplatin was evaluated in the human orthotopic ovarian carcinoma mouse xenograft model HOC-22. While control mice had a median survival time of 30 days, treatment with RO 28-2653 for three weeks, or Cisplatin for two weeks as single agents, resulted in an increase in lifespan of 63% and 95%, respectively. When used in combination, however, an increase in lifespan of 263% versus vehicle and 86% versus Cisplatin alone was observed (Fig. 1). Thus, RO 28-2653, when given in combination with Cisplatin,

was able to potentiate its anti-tumor effect significantly and increase the survival time of the animals.

Combination of RO 28-2653 with Paclitaxel

The activity of RO 28-2653 in combination with Paclitaxel was evaluated in the human subcutaneous colon carcinoma mouse xenograft model HCT 116 Cl 5.5 with primary tumor size as the endpoint. Animals from the Paclitaxel monotherapy group had an inhibition of primary tumor growth by 43% and 75% at the doses of 11.5 and 22.5 mg/kg, respectively. RO 28-2653 monotherapy resulted in the inhibition of primary tumor growth by 74% at the dose of 45 mg/kg. Combination therapy with both Paclitaxel and RO 28-2653 significantly inhibited primary tumor growth by 72% and 91% for the Paclitaxel doses of 11.5 and 22.5 mg/kg, respectively, with a dose of 45 g/kg for RO 28-2653 (Fig. 2). Thus, the combination treatment of RO 28-2653 with Paclitaxel resulted in a significant benefit for the experimental animals with respect to primary tumor size.

Combination of RO 28-2653 with Gemcitabine

The activity of RO 28-2653 in combination with Gemcitabine was evaluated in the human orthotopic pancreas carcinoma mouse xenograft model PancTu1 with primary tumor size and number and size of metastases as endpoints. Animals from the Gemcitabine monotherapy group had an inhibition of primary tumor growth by 85%. RO 28-6253 monotherapy resulted in the inhibition of primary tumor growth by 66%. Importantly, combination therapy with both Gemcitabine and RO 28-2653 significantly inhibited primary tumor growth by 94% (Table 1). With respect to the number of metastases, in the untreated or vehicle treated control groups an average of 5.1 and 4.6 metastases per animal was found. While RO 28-2653 treatment reduced these numbers to an average of 2.5 metastases per animal, and Gemcitabine monotherapy to 0.4 metastases, combination treatment with Gemcitabine plus RO 28-2653 reduced this number even further to 0.08 metastases per animal (one single metastasis in the entire treatment group) (Table 2). This is a further 5-fold reduction of the number of metastases beginning at an already low level, which makes this reduction even more impressive. This antimetastatic effect could be, at least in part, due to anti-angiogenic effects exerted by the gelatinase-

inhibitor. In fact, a defect in neo-angiogenesis has been described for gelatinase B defective mice, thus corroborating this hypothesis.

Table 1

		No treatment n=9	Vehicle 1 + 2 n=10	Gemcitabine + Vehicle 2 n=13	Ro28-2653 + Vehicle 1 n=13	Gemcitabine + Ro28-2653 n=13
Tumor take rate	Primary tumor	9/9	10/10	13/13	13/13	13/13
Volume	Primary tumor	Vm=293(±79) mm ³	Vm=333(±87) mm ³	Vm=51(±14) mm ³	Vm=112(±46) mm ³	Vm=20(±4) mm ³
Necrosis	Primary tumor	0/9	0/10	4/13	1/13	9/13
Body weight		m=10 (±5)%	m=11 (±7)%	m=2 (±5)%	m=5 (±4)%	m=1 (±4)%

- 5 Effect of the combination of RO 28-2653 and Gemcitabine on primary tumor volume in the orthotopic PancTul pancreas cancer xenograft model. Mice were treated with RO 28-2653 with daily oral doses of 45 mg/kg from day 7 until day 30. Gemcitabine treatment consisted of one intraperitoneal dose of 2.2 mg/kg every second day from day 7 to day 30.

Table 2

	No treatment n=9	Vehicle 1 + 2 n=10	Gemcitabine + Vehicle 2 n=13	Ro28-2653 + Vehicle 1 n=13	Gemcitabine + Ro28-2653 n=13
Metastasis					
Lung/ Mediastinum	7/9	4/10	0/13	2/13	0/13
Liver, in parenchyme	3/9	3/10	1/13	3/13	0/13
Liver, on serosa	1/9	1/10	1/13	2/13	0/13
Liver hilus	1/9	2/13	0/13	4/13	0/13
Kidneys/Adrenal gland (capsule)	4/9	3/10	0/13	1/13	0/13
Spleen (serosa), gastrosplenic ligament	3/9	3/10	0/13	0/13	0/13
Lymph nodes in mesentery	2/9	2/10	0/13	2/13	0/13
Mesentery < 3 metastasis(2 mm ³)	1/9	0/10	0/13	0/13	0/13
Mesentery 3-20 metastasis(1-18 mm ³)	7/9	7/10	0/13	5/13	0/13
Ligament of the uterus / testis (serosa), seminal vesicles	5/9	3/10	0/13	0/13	0/13
Diaphragm	3/9	5/10	0/13	3/13	0/13
Pelvis	1/9	3/10	0/13	0/13	0/13
Site of surgical incision					
Small < 10 mm ³	0/9	1/10	2/13	2/13	1/13
Medium < 50 mm ³	0/9	1/10	1/13	3/13	0/13
Large 80-280 mm ³	8/9	8/10	0/13	6/13	0/13

Effect of the combination of RO 28-2653 and Gemcitabine on metastatic spread in the orthotopic PancTu1 pancreas cancer xenograft model. Mice were treated with RO 28-2653 with daily oral doses of 45 mg/kg from day 7 until day 30. Gemcitabine treatment consisted of one intraperitoneal dose of 2.2 mg/kg every second day from day 7 to day 30.

Combination of RO 28-2653 with Etoposide

5 The activity of RO 28-2653 in combination with Etoposide was evaluated in the rat syngeneic orthotopic prostate carcinoma model MatLyLu with primary tumor size as endpoint. Animals from the Etoposide monotherapy group showed inhibition of primary tumor growth by 35% as compared to the vehicle-treated animals. RO 28-6253 monotherapy resulted in the inhibition of primary tumor growth by 86%. Importantly, the combination therapy with both Etoposide and RO 28-2653 significantly inhibited primary tumor growth by 92% (Fig. 3).

List of References

- Brown, P.D., Medical Oncology 14 (1997) 1-10
Drummond, A.H., et al., Ann. N.Y. Acad. Sci. 878 (1999) 228-235
Fletcher, L., Nature Biotechnology 18 (2000) 1138-1139
5 Giavazzi, R., et al., Clin. Cancer Res. 4 (1998) 985-992
Johansson, N., et al., Cell. Mol. Life Sci. 57 (2000) 5-15
Vu, T.H., et al., Cell 93 (1998) 411-422
WO 01/25217
WO 97/23465

- 10 -

Patent Claims

1. Use of a gelatinase inhibitor for the preparation of a medicament for the treatment of tumor growth or inhibiting metastases in combination with an antitumor agent.
- 5 2. Use according to claim 1, wherein the gelatinase inhibitor is 5-(4-biphenyl)-5-[N-(4-nitrophenyl) piperazinyl] barbituric acid.
3. Use according to claims 1 or 2, wherein the antitumor agent is a compound selected from the group consisting of Cisplatin, Paclitaxel, Vinblastin, Mitomycin, Gemcitabine, Etoposide, Doxetaxel, Carboplatin, Irinotecan,
10 Topotecan, Navelbine, Doxorubicin, Epirubicin, Oxaliplatin, 5-Fluoruracil, Capecitabine, 5-UFT, Herceptin, alpha interferon
4. Use according to claims 1 to 3, whereby the gelatinase inhibitor and the tumor agent are administered simultaneously.
5. Use according to claims 1 to 3, whereby the gelatinase inhibitor and the
15 tumor agent are administered sequentially.
6. Use according to claims 1 to 4, whereby the gelatinase inhibitor and the anti-tumor agent are part of a kit.
7. Use according to claims 1 to 6, wherein the gelatinase inhibitor is present as a tablet or capsule.

Fig. 1

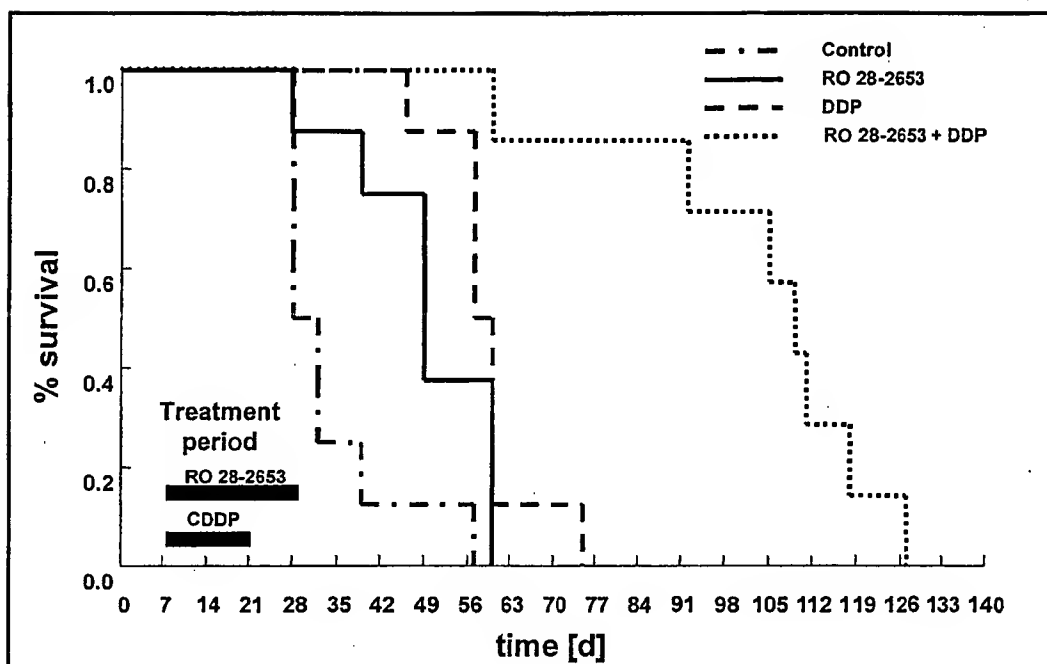
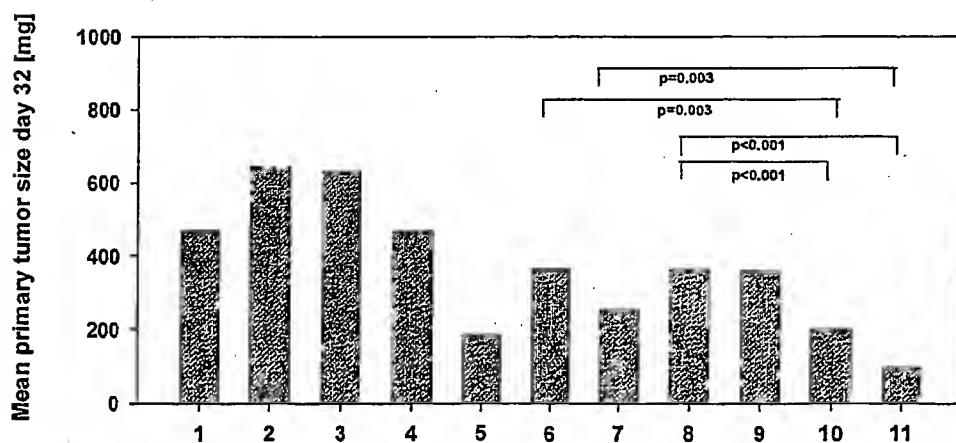
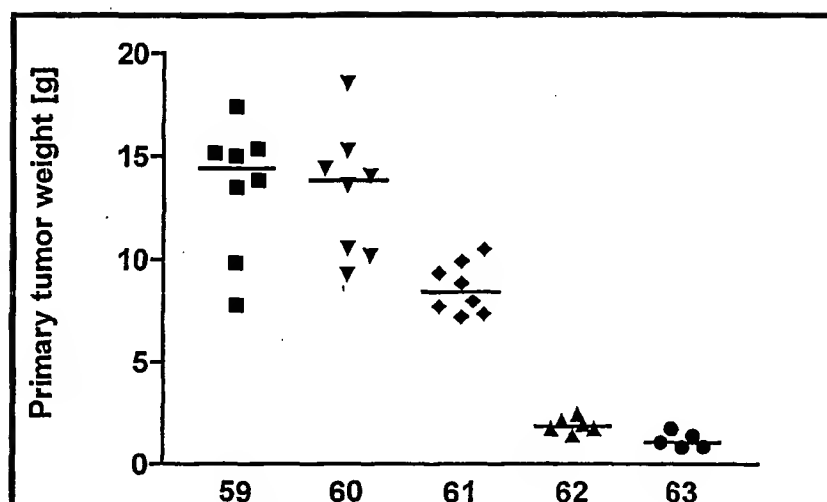


Fig. 2



	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group 10	Group 11
Treatment period (23 days):	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle
Dosage:				11.25 mg/kg	22.5 mg/kg				45.0 mg/kg	45.0 mg/kg	45.0 mg/kg
Application mode:	1x1, p.o.	q7d3 weeks, i.v.	1x1, p.o.	q7d3 weeks, i.v.	q7d3 weeks, i.v.	1x1, p.o.	1x1, p.o.	q7d3 weeks, i.v.	1x1, p.o.	q7d3 weeks, i.v.	q7d3 weeks, i.v.
p-value				0.047	<0.001	<0.001	<0.001	<0.001	0.038	<0.001	<0.001
Inhibition %				38	77	43	75	47	33	72	91

compared to relevant vehicle group

Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04744

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K33/24 A61K31/70 A61K31/515 A61K45/06 A61P35/04
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 37107 A (SEARLE & CO) 29 June 2000 (2000-06-29) page 21-22	1-7
Y	page 76; claims 1-6, 8-10, 12, 14, 21, 26, 29; table 1 page 127, paragraph 3 page 170, paragraph 5; example 7 page 43-44	1, 7
Y	page 45; table 1 page 80, line 13-15 page 95; claim 55 --- -/-	1, 7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SHALINSKY, DAVID R. ET AL: "Marked antiangiogenic and antitumor efficacy of AG3340 in chemoresistant human non-small-cell lung cancer tumors: single agent and combination chemotherapy studies"</p> <p>CLIN. CANCER RES. (1999), 5(7), 1905-1917, XP001042322</p> <p>page 1916</p> <p>page 1906, right-hand column</p> <p>---</p>	1,3,5
X	<p>YIP, DESMOND ET AL: "Matrix metalloproteinase inhibitors: applications in oncology"</p> <p>INVEST. NEW DRUGS (1999), 17(4), 387-399, XP001058160</p> <p>page 394, right-hand column, paragraph 5</p> <p>-page 395, left-hand column, paragraph 4</p> <p>page 394, right-hand column, paragraph 3</p> <p>page 396, right-hand column, paragraph 2</p> <p>---</p>	1,3-5
X	<p>SHALINSKY D R ET AL: "BROAD ANTITUMOR AND ANTIANGIOGENIC ACTIVITIES OF AG3340, A POTENT AND SELECTIVE MMP INHIBITOR UNDERGOING ADVANCED ONCOLOGY CLINICAL TRIALS"</p> <p>ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, NEW YORK ACADEMY OF SCIENCES, NEW YORK, NY, US,</p> <p>vol. 878, 1999, pages 236-270, XP001007565</p> <p>ISSN: 0077-8923</p> <p>page 238, paragraph 1</p> <p>page 261, paragraphs 3,4</p> <p>page 264-265</p> <p>---</p>	1,3-7
X	<p>GIAVAZZI ET AL: "Batimastat, a synthetic inhibitor of matrix metalloproteinases, potentiates the antitumor activity of cisplatin in ovarian carcinoma xenografts"</p> <p>CLIN. CANCER RES.,</p> <p>vol. 4, 1998, pages 985-992, XP001042280</p> <p>cited in the application</p> <p>page 989, right-hand column, line 7-11, paragraph 6; figure 1</p> <p>---</p>	1,3-5
X	<p>WO 99 52889 A (PFIZER PROD INC)</p> <p>21 October 1999 (1999-10-21)</p> <p>page 8, line 13-16; claims 8,10</p> <p>page 1, line 10,11</p> <p>page 2, line 31</p> <p>---</p> <p style="text-align: center;">-/--</p>	1,3-5

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PCT/EP 02/04744

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KELLY, KAREN: "New chemotherapy agents for small cell lung cancer" CHEST (2000), 117(4, SUPPL. 1), 156S-162S, XP001064989 the whole document</p> <p>-----</p>	1,3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/04744

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 AND 3-7 relate to uses involving a compound defined by reference to a desirable characteristic or property, namely inhibiting gelatinase.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action and/or its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the claims, with due regard to the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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